Summary

The aim of this thesis is to understand the interesting facets of de novo heme and its functional significance in the entire life cycle of malaria parasite by generating the knock outs for enzymes involved in parasite de novo heme biosynthetic pathway. Since the parasite heme-biosynthetic enzymes differ significantly from their host counterparts, the pathway offers newer drug targets. This study is also intended to test the potential of the parasite heme-biosynthetic pathway knock out sporozoites as liver stage vaccine candidate. The PhD thesis entitled ‘A detailed study addressing the functional significance of de novo heme biosynthetic pathway in the entire life cycle of malaria parasite and its potential as drug target and vaccine candidate’ is presented as five chapters.

Chapter1: An Overview of malaria parasite biology

This is an introductory chapter comprise of: A brief history of malaria, life cycle of Plasmodium and developmental stages in parasite life cycle, Antimalarial drugs and Vaccine candidates, Metabolic pathways as drug target in Plasmodium.

Chapter 2: De novo heme biosynthetic pathway in malaria parasite

This is an introductory chapter for de novo heme biosynthetic pathway in malaria parasite and comprise of: Heme, Heme biosynthesis and heme biosynthetic pathway in malaria parasites.

Chapter3: Contribution of host heme versus de novo biosynthetic heme in asexual stage development of malaria parasite

This chapter has the results pertaining to the in vitro radiolabeling of heme in mouse reticulocytes infected with P. berghei WT and knock out parasites. Based on the radiolabeling of host heme in mouse reticulocytes and the parasite heme in WT but not in Knock out parasites, the contribution of host v/s parasite de novo heme in the asexual stage development was studied.

Chapter4: Essentiality of de novo heme biosynthesis in the sexual and liver stages of malaria parasite

This chapter has the results pertaining to the ability of knock out parasites to undergo sexual and liver stage development. The knock out parasites were unable to form sporozoites in the
mosquitoes, and ALA supplementation to mosquitoes restored the formation of PbALASKO sporozoites, but these sporozoites failed to subsequently infect mice to form intraerythrocytic-stage parasites in blood. However, PbALASKO sporozoites could infect mice only when the mice received ALA supplement. Based on these results, the essentiality of de novo heme biosynthesis in the sexual and liver stage development was studied.

Chapter 5: De novo heme biosynthetic pathway gene knockout parasite as genetically attenuated sporozoite vaccine

This chapter has the results pertaining to immunizing mice with PbALASKO sporozoites and examining liver stage protection. The numbers of memory CD8+ T cells were found to be increased in PbALASKO immunized mice in comparison with naïve mice post immunization showing that the liver stage protection in PbALASKO immunized mice is mediated by CD8+ based memory response. Based on results obtained, the potential of PbALASKO parasite as a genetically attenuated sporozoite vaccine candidate was demonstrated.